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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,562	02/22/2000	Gerard Housey	395/35	3061

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
GUZO, DAVID	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,562	HOUSEY, GERARD	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004 and 10 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/8/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Applicants' claim for benefit under 35 USC 120 for the 07/154,206 application, filed 2/10/88 (U.S. Patent 4,980,281) is acknowledged. However, since the instant specification (and the specifications of the parent applications) do not provide an enabling disclosure or written description for the claimed invention and given that priority for a claimed invention can only be granted when the parent application(s) complies with 35 USC 112, 1st paragraph, applicants are granted priority only back to the filing date of the instant application.

The Opinion rendered 12/4/03 in Bayer AG v. Housey Pharmaceuticals, Inc. and provided by applicant in an IDS filed 1/8/04 is acknowledged.

The 102(b) rejection over Riedel et al. is withdrawn in view of applicant's arguments. It is noted that the 37 CFR 1.131 Declaration of Dr. Housey, which attempted to overcome the outstanding 35 USC 102(b) rejection (which applicants argued was a 102(a) rejection) by swearing behind the Riedel et al. reference was, in and of itself, not sufficient. The Declaration did not provide sufficient evidence that Dr. Housey had conceived of the claimed invention prior to the publication date of the Riedel et al. reference. The only evidence presented concerning conception of the claimed invention involved a diagram of possible methods of entry of D-amino acids into cells and the results of a competitive inhibition experiment that would support a particular model of D-amino acid transport. It is unclear how this would have provided conception of the claimed method for determining whether a chemical agent is a direct

inhibitor of an enzyme in a cell. However, as priority has been granted back to the instant filing date, the issue is moot.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33-34, 36, 43-44, 46-47, 49, 88-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Uehara et al.

Applicant claims methods for determining whether a chemical agent is a direct inhibitor or activator of a POI (enzyme) in a cell where expression of the POI results in a phenotypic characteristic in the cell, said method comprising providing a test mammalian cell line which produces said POI and exhibits a phenotypic response to the POI and wherein the level of the enzyme in the cell is maintained such that the cell is capable of exhibiting the phenotypic response following removal of the test chemical, providing a second mammalian cell line which is alike to the first cell line but which produces the POI at lower levels or not at all, incubating the test chemical with the first and second cell lines, comparing the phenotypic responses of the first and second cell lines to the test chemical.

Uehara et al. (cited by applicants, Jpn. J. Cancer Res., 1985, Vol. 76, pp. 672-675, see whole document, particularly the Abstract, paragraph bridging pp. 672-673, paragraph bridging pp. 673-674) recites a method for determining whether a chemical

agent (herbimycin) is a inhibitor of an enzyme ($p60^{src}$) in a cell whose production (at culture conditions of 33 degrees C) by the cell evokes a responsive change in a phenotype of the cell (change in cell morphology), said method involving incubating the chemical agent (herbimycin) with a first cell line which produces said enzyme and wherein the level of the enzyme in the cell is maintained such that the cell is capable of exhibiting the phenotypic response following removal of the chemical agent, and a second cell line (control cells not containing the $p60^{src}$ or cells containing the enzyme and not treated with herbimycin) and comparing the responses of the two cell lines to the treatment. The gene encoding $p60^{src}$ is under control of a promoter since it is expressed in the transformed cells. Herbimycin inherently binds directly to the $p60^{src}$ and inhibits auto and trans-phosphorylation activities of $p60^{src}$ which are associated with cellular changes associated with transformation (this was definitively proven by Uehara et al., Biochem. Biophys. Res. Comm., 1989, Vol. 163, No. 2, pp. 803-809, cited by applicants). It is noted that secondary evidence showing an inherent feature of a claimed invention can be cited in a 35 USC 102 rejection (See MPEP 2131.01). Uehara et al. therefore teaches the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method of inhibiting or activating a particular protein or enzyme comprising determining whether a chemical agent that directly interacts with the protein or enzyme is an inhibitor or activator of the protein or enzyme and exposing a cell containing the enzyme to the chemical agent so as to inhibit or activate the enzyme.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor, but rather is a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) Unpredictability of the art. The art in this area is unpredictable. In order to practice the claimed invention the skilled artisan must be able to distinguish between chemical agents which act indirectly to inhibit or activate the target protein or enzyme of interest (P01) from those agents which directly interact with the PO1 so as to inhibit or activate the POI. Applicant does indicate that: "Substances which specifically inhibit or inactivate the POI may be distinguished from substances which affect cell morphology or growth by other mechanisms in that they have a greater effect on the test lines than

on the control lines." (Specification, p. 5). Applicant also recites: "What we are looking for is a increase in the phenotypic change exhibited by the cell which becomes greater with increased expression of the PO1. We call this a "graded response" and it is by this specialized response that we distinguish inhibitors or activators of the PO1 from agents that act upon other cell metabolites to effect a phenotypic change." (Specification, p. 12). However, this disclosure does not provide guidance on how the skilled artisan would distinguish between chemical agents which directly interact with the POI vs. those which affect the POI by indirect means. For example, if the skilled artisan would attempt to practice the claimed invention to identify inhibitors or activators of the human bladder c-Ha-ras oncogene (See Hsiao et al., cited by applicants, Mol. Cell. Biol., 1986, Vol. 6, No. 6, pp. 1943-1950) and contacted cells overexpressing the c-Ha-ras oncogene as well as cells which did not express the oncogene, with compounds such as TPA or teleocidin, etc. the skilled artisan would observe a greater phenotypic effect on the test cell line compared with the control line. Given applicant's disclosure, the skilled artisan would identify TPA or teleocidin as a chemical agent which **directly interacts** with c-Ha-ras and serves as an activator of c-Ha-ras. This would not be correct because TPA or teleocidin does not directly interact with c-Ha-ras but instead may function by interacting with cellular protein kinase C receptors or other cellular receptors which in turn may interact in some fashion with the c-Ha-ras oncogene product (p21). Applicant presents no teachings on how the skilled artisan would be able to distinguish between false positive results (as discussed above) and results which would emanate from a direct interaction between the POI and the chemical agent.

Alternatively, applicant presents no disclosure on how the skilled artisan would distinguish between false negative results from true negative results. For example, if the POI was a protein or enzyme in the nucleus and the chemical agent was a compound able to activate or inhibit the PO1 but was unable to enter the cell or the cell nucleus, or was chemically modified by the cell upon uptake, a false negative result would result. Indeed, the skilled artisan, in order to practice the claimed invention, would have to perform **additional, undisclosed, experimentation** to determine whether the chemical agent initially identified as a inhibitor or activator actually interacts directly with the POI and serves as an a inhibitor or activator as a consequence of said direct interaction. Given the broad scope of the claims, reading on methods of inhibiting or activating any protein or enzyme expressed in any mammalian cell and given that many POIs of particular interest (i.e. receptors, oncogenes, DNA or RNA binding proteins, etc.) which are involved in cell metabolism or cell growth are components of extremely complex metabolic and physiological pathways and can be influenced by multiple factors which do not directly interact with the POI, it must be considered that the art with regard to methods of inhibiting or activating particular enzymes or proteins in cells is unpredictable.

2) State of the art. The art in the area of developing methods of inhibiting or activating proteins or enzymes (POIs) in cells by chemical agents that directly interact with said POIs and monitoring responsive changes in phenotypic characteristics of the cell evoked by production of the POI is poorly developed.

3) Number of working examples. Applicant presents no working examples of the claimed invention wherein a method for inhibiting or activating a particular POI in a cell is accomplished by determining whether a chemical agent that directly interacts with the POI is an inhibitor of said POI. Applicant's disclosure provides no mechanism which would enable the skilled artisan to distinguish between chemical agents which interact indirectly with POI and agents which interact directly with the POI.

4) Amount of guidance provided by applicants. As noted above, applicant provides no guidance on distinguishing a chemical agent which directly interacts with the POI vs. an agent which interacts in some other indirect fashion with the POI. Without such a teaching, the skilled artisan would be unable to practice the instant claims.

5) Scope of the claims. The claims are extremely broad and read on methods of inhibiting or activating any protein or enzyme in a cell.

6) Nature of the invention. The invention involves a complex area in the screening art involving the identification of agents which inhibit or activate proteins or enzymes of interest in cells.

7) Level of skill in the art. The level of skill in the art is high; however, given the lack of guidance provided by applicant, given the unpredictable nature of the art with regard to attempting to identify inhibitors or activators of proteins involved in complex metabolic and biochemical pathways and given the broad scope of the claims, it must be considered that the skilled artisan would have had to have practiced essentially trial and error experimentation in order to attempt to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would need to have conducted undue and excessive experimentation in order to practice the claimed invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has not provided a written description of a method of inhibiting or activating a particular POI wherein said method comprises the step of determining whether a chemical agent that **directly interacts** with the POI is an inhibitor or activator of said POI. Applicant has not described a method which is capable of determining whether any given chemical agent **directly interacts** with the POI and in doing so serves as an inhibitor or activator of the POI. Applicant discloses a method for inhibiting or activating a PO1 which does not discriminate between chemical agents which directly or indirectly interact with the POI. Successful practicing of the claimed invention would require additional, undisclosed method steps which have not been described.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-89 are vague in the recitation of the phrase "...wherein the level of the enzyme in the cell is maintained such that the cell is capable of exhibiting the phenotypic response following removal of a direct activator or inhibitor of the enzyme..." because it is unclear if the enzyme (POI) must be maintained **in an active form** in the cell when in the presence of (and bound to) the inhibitor. It is unclear if the language encompasses the circumstance wherein the inhibitor binds to and inactivates the enzyme (and results in a phenotypic change, i.e. reversion to a normal phenotype) but when the inhibitor is removed, the cell is capable of producing and maintaining the enzyme so as to produce the phenotype resulting from expression of the target enzyme (POI).

Also, the claims are vague in that the methods do not recite a step(s) which refers back to or recapitulates the preamble of the claim. The preamble of the claims recites a method for determining whether a chemical agent is a direct inhibitor or activator of an enzyme in a cell, but the method claims end with the step of comparing the phenotypic responses of the first and second cells to the chemical agent or determining whether the test cell exhibits a change in the phenotypic characteristic in response to the chemical agent. No step recites the relevance of these comparisons or observed changes to whether a chemical agent is a direct inhibitor or activator of the

enzyme, i.e. no step(s) recites the correlation between the phenotypic changes observed and whether the chemical agent is a direct inhibitor or activator of the enzyme. The metes and bounds of the claimed subject matter are therefore unclear because the claims are incomplete.

Applicants' amendments to the claims and arguments traversing the previous 35 USC 112, 1st paragraph (written description) rejections are noted. Said rejections are withdrawn.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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David Guzo
April 19, 2004

DAVID GUZO
PRIMARY EXAMINER